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(57) Abstract

The present invention provides devices and methods for perfusing organs by controlling either the perfusion pressure or the perfusate flow rate. The operator may select either method of perfusion control. Also provided are devices and methods for perfusing multiple organs simultaneously on the same device.

ORGAN PERFUSION DEVICE

BACKGROUND OF THE INVENTION

The present invention relates generally to organ perfusion devices and techniques of organ perfusion. In particular, the perfusion devices may simultaneously perfuse more than one organ in an independent manner. The perfusion devices may also perfuse organs at either constant perfusion pressure or constant perfusate flow rate, at the discretion of the operator. Methods are provided for simultaneously perfusing multiple organs, perfusing organs on devices capable of regulating both the flow rate and pressure of a perfusate, and measuring the effect of a stimulus, chemical or otherwise, on organ function.

Maintaining viability of animal organs following removal of the organ from the animal's body (ex vivo viability) or during isolation of the organ from the animal's natural circulation is of great importance for medicine, pharmacology, and physiology. Traditionally, excised solid organs have been maintained through a combination of hypothermia and exposure to nutrient solutions. Hypothermia decreases the metabolic activity of cells within the organ. The decreased metabolic activity lowers the cells' demand for nutrients and oxygen while concurrently suppressing the production of toxic waste products. Exposure to nutrient solutions serves two functions. First, the cells of the isolated organ may be exposed to nutrients and/or oxygen. Second, toxic waste products are removed as the solution is washed over or through the organ.

Devices previously used for maintaining ex vivo organ viability have relied on three methods of nutrient solution exposure. In perfusion, the isolated organ is bathed in a nutrient containing culture medium. While this method is effective for bone marrow or other non-solid organ preservation, perfusion does not optimize solid organ

for organ transplant and preservation neither monitor the physiological state of the transported organ nor respond to organ changes by altering the preservation conditions under which the organ is being maintained. Thus, preventable organ damage may occur during transport. As more diseases are treated by transplantation, especially with fragile organs, optimizing preservation conditions will assume even greater importance.

Also, ex vivo therapies are being developed for the treatment of various diseases. For example, ex vivo lymphocyte stimulation and activation has been employed for the treatment of AIDS-related diseases. Ex vivo therapy may also provide a means to expose an organ to high doses of a therapeutic modality while protecting other organs from the therapy. Cancer chemotherapy is one such example. Solid tumors, such as hepatomas, do not respond well to doses of chemotherapeutic agents that are tolerable to the bone marrow. Ex vivo treatment of the liver could provide very high drug doses to the tumor while sparing the bone marrow. For effective ex vivo treatment, however, the organ must be perfused so as to optimize viability. Hence, the perfusion device must be capable of delivering adequate levels of perfusate to the organ, monitoring the function and viability of the treated organ, and responding to changes in organ function during treatment. Presently available perfusion devices can not monitor and respond to physiological changes in the isolated organs.

Circulatory isolation of organs within the body is also desirable for medical treatment. If an organ can be perfused in isolation while remaining in the body, many of the advantages of ex vivo therapy may be realized with less morbidity. Catheters that selectively occlude blood vessels leading into and out of a solid organ may be used to selectively perfuse the organ with a therapeutic substance. As in ex vivo therapy, high levels of a drug could be delivered to the diseased organ without risking potentially toxic side-effects in other organs. Also like ex vivo therapy, the

met by cell culture perfusion devices, however. As noted above, constant pressure perfusion can often result in differences in organ perfusion volume. This difference in perfusate volume can affect the organ's viability and function. A device which provides constant flow perfusion would alleviate this problem. Unfortunately, constant flow perfusion is not always appropriate, such as during extreme vasoconstriction or vasodilation. Comparison to other research often requires constant pressure perfusion also. Hence, it would be preferable for perfusion devices to operate under either constant pressure or constant flow. Perfusion devices available in the art can only perfuse by constant pressure or constant flow.

Physiological or pharmacological research also requires that treated or stimulated organs be compared to control organs. Ideally, the control organ receives identical perfusate at the same temperature, pH, pO_2, pCO_2, etc. Unfortunately, slight variations in perfusate compositions often occur which can alter the normal organ function. Because the baseline functions of the control organ and the test organ are altered by the perfusate differences, it is difficult to accurately interpret test data. A means to deliver perfusate to both organs from the same source would overcome this difficulty and allow for more accurate physiological and pharmacological assessments. Presently available perfusing devices do not fulfill this need.

Even though the test organs and control organs may not be studied under identical conditions, it is necessary to gather both sets of data in modern research. Conducting two sets of tests is time consuming and laborious for laboratory personnel. A device which would study both the test organ and control organ simultaneously would provide a means to increase laboratory productivity and lower the cost of research. In light of the steadily rising cost of research and the increasing scarcity of funding, a means to generate both test data and control data simultaneously is of great importance.

BRIEF DESCRIPTION OF THE FIGURES

Fig. 1 illustrates a schematic diagram of a perfusion device for perfusing multiple organs constructed in accordance with the principles of the present invention.

Fig. 2 illustrates a schematic diagram of a perfusion device capable of altering perfusion characteristics so as to optimize organ viability for perfusing a single organ constructed in accordance with the principles of the present invention.

DETAILED DESCRIPTION OF THE SPECIFIC EMBODIMENTS

According to the present invention, devices and methods are provided for perfusing solid animal organs. Solid organs are those organs which have an identifiable vascular system for carrying blood with separate inflow and outflow vessels. Solid organs which may be perfused by the present invention include hearts, kidneys, livers, thyroids, lungs, intestines, pancreases, reproductive organs, brains, spleens and the like. The organs of any animal may be perfused, provided that the vascular inflow vessel is of sufficient size to accommodate a fluid conduit. The organ source will generally be mammalian, such as mouse, rat, dog, cat, or human, although other animal species may be appropriate for different applications.

One embodiment of the present invention provides an organ perfusion device having a source of a perfusate, a first fluid conduit fluidly connecting the source of a perfusate to an upstream pump, a second fluid conduit for fluidly connecting the upstream pump to an organ, a means to regulate the pressure of the perfusate in the second fluid conduit, and a means to regulate the flow rate the perfusate through the second fluid conduit.

As used herein, when component A is "upstream" or "proximal" to component B, unrecycled fluid from the source of the perfusate flows through component A before flowing through component B during the normal operation of devices of the present invention. Likewise, component B is "distal" or

organ viability. A fluid conduit connects the reservoirs to the mixing means. By "fluid conduit", it is meant any means of directing the fluid from one component of the device to another component of the device which, except for the proximal and distal openings which connect to the device components, is closed. While generally the fluid conduit means will be tubing, such as polyethylene, silicone, or Tygon® tubing, alternative means are also envisioned, e.g., bored channels through solid supporting structures.

Conveniently the mixing means may be an electronic valve, such as the Cavro Electric Motor Valve, Cavro Corporation. Other mixing means are acceptable, e.g., the device described in U.S. Patent No. 4,629,686, incorporated herein by reference. Persons of skill in the art will readily appreciate that different valves are appropriate for different uses depending on the size of the organ being perfused, viscosity of the perfusate, cellular content of the perfusate, etc. The electronic valve independently controls the flow rate of each different fluid into a common flow line such as polyethylene, silicone, or Tygon® tubing, or the like. The electronic valve may be controlled directly by the operator or through electronic means, such as a computer which alters the composition of the perfusate mixture in response to externally created signals. Alternatively, the mixing means may be a manual valve device.

After mixing has occurred, or directly from a single reservoir as appropriate, the perfusate may flow through filters, an oxygenator, and/or a heat exchanger, all connected by fluid conduits. The filters may also include a one way valve to avoid backflow into the reservoirs. Suitable filters include, e.g., The Whatman 6702-3600 or Gilman 12158.

The oxygenator may be a membrane oxygenator, such as Sci. Med Ultrox I, and the like, or a hollow fiber oxygenator, such as CD Medical Oxy 10 and Oxy 1 or Unisyn Fibertec Cell-Farm Hollow Fibers Oxygenator and the like. The gas introduced by the oxygenator will generally be O_2, CO_2, or a mixture thereof. The pH of the perfusate may be adjusted by altering

The output of the pump is determined by pump speed. The pump speed is regulated in two modes, perfusion pressure or perfusate flow rate in the second fluid conduit. During perfusion, the perfusion pressure or the perfusion flow rate may be varied or held constant. The mode may also be changed, either during perfusion or otherwise. Hence, the pump speed may be changed in response to functional characteristics of the organ or regulated to a constant flow or a constant pressure. When controlled by a computer, the pump speed may be controlled so as to provide either constant perfusion pressure or constant flow rate, provided the uncontrolled mode remains within a defined range. If the uncontrolled mode leaves the predetermined range, the controlled mode will be adjusted. For example, if the organ is being perfused at a constant perfusion pressure, the flow rate may be programmed so as to not decrease below a certain level. If the organ vasoconstricts and the flow rate decreases below the allowed level, the perfusion pressure will be increased to maintain the minimum allowable flow rate.

The pump speed is controlled by a pump speed control mechanism. The pump speed control mechanism will generally be responsive to inputs from a computer or other electronic source. Inputs from the electronic source controls the pump speed control mechanism which in turn controls the speed of the pump. In this way, the pump output is controlled by inputs to the pump speed mechanism. Alternatively, the pump speed control mechanism may be responsive to manual inputs.

After exiting the pump, the perfusate is channeled into a second fluid conduit to the organ. The second fluid conduit terminates in the arterial system of the organ. Generally, the second fluid conduit communicates directly with the main artery of the organ, e.g., the renal artery in human kidneys, the testicular artery in human testes, etc. In organs having a plurality of arterial inputs or accessory circulation, e.g., the human heart, human lung, etc., each arterial input may be perfused from the pump by way of branching the second

perfusate, to the heat exchanger to control the temperature of the perfusate, and the electronic valve to control the chemical composition of the perfusate. Software is commercially available which provides these functions, such as Lab Windows®, produced by National Instruments of Austin, Texas, which can also be customized by the producer to meet individual needs.

After the perfusate leaves the second fluid conduit, it travels through the circulatory system of the organ. The organ may be contained in an organ chamber. The organ chamber may be environmentally controlled if appropriate. The organ may also be immersed in the perfusate or another solution the organ chamber. Immersion in a solution provides a means to more precisely control organ temperature and fluid balance. The solution may be static or flow over the organ such as described in U.S. Patent No. 4,395,492, incorporated herein by reference.

As the perfusate flows through the organ's circulation, it is gathered by the venous system and exits an organ vein, e.g., the human renal vein. The perfusate may openly drain from the organ or channeled into a third fluid conduit. The third fluid conduit may include a downstream sensor similar to the upstream sensor. The perfusate characteristics measured by the downstream sensor can indicate functional and metabolic attributes of the organ. For example, if a kidney is being perfused, the Na and Cl concentrations and the osmolality can provide an indication of the perfusion and viability of the kidney since the renal cortex will filter electrolytes and alter the composition of the perfusate when the kidney is viable and fully perfused. When the kidney is ischemic, intra-renal circulatory shunts occur which alter the function of the kidney and hence the outflowing perfusate. Likewise, ischemia in a perfused heart can be detected by an increase in the lactate concentration of the outflowing perfusate.

The downstream sensor will generate signals representing the measured perfusate characteristics and transmit the signals to a decoding device. The decoding device

provides a means to perfuse each different organ with identical perfusate or with perfusates differing in only one characteristic or component. Generally the device will be capable of perfusing two organs, although this is not critical and may vary. Each organ is supplied with perfusate propelled by separate pumps. The pump speed of each pump is controlled by separate pump speed control mechanisms so that the pump speed of each pump may be controlled independently from each of the other pumps. The pumps may independently operate in either constant pressure mode or constant flow rate mode. The perfusion pressure or the perfusion flow rate to each organ may be independently regulated by this means.

In embodiments providing for the perfusion of multiple organs, the second fluid conduit is branched. The second fluid conduit has a single proximal end connected to the source of a perfusate. Distal to the second fluid conduit's proximal end, the second fluid conduit branches into multiple passages so that each passage fluidly connects the branch point to each separate pump thereby connecting each pump to the source of the perfusate. Each multiple passage may include an oxygenator or heat exchanger so that the temperature, pH, pO_2, pCO_2, and the like may be independently regulated to each pump and thus to each organ. In this manner it is possible to vary one characteristic of the perfusate and study the effect of that variation on organ function.

Methods for perfusing organs employing devices which can regulate both the perfusate flow rate or the perfusion pressure are also provided. Multiple organs may be simultaneously perfused on a single device by the disclosed methods. The methods generally comprise connecting the arterial system of each organ to separate pumps by means of at least one fluid conduit, which pumps are connected to a source of a perfusate and administering the perfusate to each organ by independently regulating each pump to adjust the pressure or flow rate of the perfusate in the fluid conduit.

A number of third fluid conduits are hermetically attached to the arterial system of each organ to be perfused.

organ. In this manner, organ viability can be optimized by prompt detection and correction of metabolic or functional abnormalities of the organ.

Methods for determining the effect of a test substance on an organ are also provided. At least two organs are perfused on a perfusion device of the present invention. One organ is exposed to the test substance by introducing the test substance into the perfusate distal to the pump. Because each organ is perfused by a separate pump, the test substance may be administered to only one organ when introduced to the perfusate downstream of the branch point in the second fluid conduit. If the test substance is introduced upstream to the upstream sensor, the concentration of the substance entering the test may also be determined. The effect on the test organ may be determined by comparing the characteristics of the perfusate leaving the test organ to those of the perfusate leaving the control organ as measured by downstream sensors. Alternatively, the effect of the substance on the test organ can be measured by means other than the characteristics of the perfusate leaving the organ, such as an intraventricular balloon to measure cardiac wall tension or contractility.

Referring now to Fig. 1, there is shown a schematic illustration of one embodiment of a perfusing device constructed in accordance with the principles of the present invention. Like reference characters will be used to indicate like elements.

The illustrated embodiment is a device for simultaneously perfusing two organs. Multiple reservoirs 1 are able to hold different solutions. The solutions flow through individual tubing 2 from the reservoirs 1 to an electronic valve 3. The electronic valve 3 regulates the flow of each different solution into a common tube 4 thereby producing the perfusate. The composition of the perfusate may be altered by changing the ratio of the flow rates of the different solutions through the electronic valve 3. As the perfusate flows through the common tube 4 it is filtered by a filter 5. Following filtration, the perfusate continues through the common tube 4

contacting the perfusate. In this manner, any of these characteristics may be regulated in the perfusate which is entering the organs 15.

The inputs produced by the computer 19 in response to signals from the upstream sensors 14 representing the temperature of the perfusate may be transmitted to the heat exchanger 8 to alter the temperature of the heat exchanger 8. The temperature of the perfusate entering the organs 15 may be adjusted in this manner.

The inputs produced by the computer 19 in response to the perfusion pressure or flow rate of the perfusate in the second fluid conduits 13 may be transmitted to upstream pump speed control mechanisms 21. The pump speed control mechanisms 21 control the speed of the upstream pumps 12. The speed of the upstream pumps 12 may be controlled independently. The computer may produce inputs which will cause the pump speed control mechanisms 21 to vary the speed of the upstream pumps 12 to regulate the perfusion pressure or the perfusate flow rate in the second fluid conduits 13 by controlling the pump speed.

An injection port 24 is located in one of the second fluid conduits 13. The injection port 24 allows for selective administration of test compound, such as a pharmaceutical, toxin, hormone, or other substance, into only one of the organs 15. The injection port is located upstream to the sensor 14 in the second fluid conduit 13. The sensor 14 may determine concentrations of the test substance in the perfusate. The single injection port 21 located downstream from the common first fluid conduit 10 provides a method of perfusing two organs 15 with a perfusate identical in all respects except the added test substance. In this manner, accurate determination of the effect of the test substance on the organ 15 is possible.

Referring now to Fig. 2, a perfusion device for perfusing a single organ constructed in accordance with the principles of the present invention is illustrated. The embodiment in Fig. 2 monitors characteristics of the perfusate

can mix the returning perfusate with solutions from the reservoirs 1 to recycle the perfusate.

The upstream sensor 14 and the downstream sensor 23 produce signals representative of the perfusate characteristics which are monitored. The signals are transmitted to a computer 19. The computer 19 may display the information represented by the signals in real time, store the information represented by the signals, or produce inputs in response to the signals. The inputs may control the gas source 7, heat exchanger 8, pump speed control mechanism 21 and/or electronic valve 3. Because the inputs are produced and varied by the computer 19 in response to the signals produced by the upstream sensor 14 and the downstream sensor 23, the computer 19 may adjust the composition and other physical characteristics of the perfusate to optimize organ viability.

The foregoing is offered primarily for purposes of illustration. It will be readily apparent to those of skill in the art that the components of the perfusion devices, the methods of organ perfusion, and other characteristics of the invention described herein may be modified or substituted in various ways without departing from the spirit and scope of the invention.

6. A device for the simultaneous perfusion of a plurality of individual organs comprising:

one or more upstream pumps equal in number to the number of individual organs being simultaneously perfused;

one or more first fluid conduits connecting each pump to a source of a perfusate; and

one or more second fluid conduits connecting the arterial system of each individual organ with a single upstream pump, wherein each upstream pump is connected to only one organ.

7. The device of claim 6, wherein each upstream pump operates at a pump speed variable to regulate the pressure or the flow rate of the perfusate in the second fluid conduit.

8. The device of claim 7, wherein the pump speed of each upstream pump is independent of another upstream pump.

9. The device of claim 6, wherein each second fluid conduit further comprises an upstream sensor which monitors the temperature, pH, pO_2, pCO_2, electrolyte concentration, flow rate, or perfusion pressure characteristics of the perfusate.

10. The device of claim 9, wherein the upstream sensor monitors two or more of said characteristics.

11. The device of claim 6, wherein the source of perfusate further comprises multiple fluid reservoirs, and a means to selectively mix the fluids from the different reservoirs.

12. The device of claim 11, wherein the means to selectively mix the fluids comprises an electronic valve.

13. The device of claim 12, wherein the electronic valve is controlled by a computer.

conduit and produces signals representing the monitored characteristics.

23. The method of claim 22, wherein the upstream sensor monitors the pressure and flow rate of the perfusate in the fluid conduit and regulates the pump thereby.

24. The method of claim 21, wherein the effect of a substance on an organ is determined by exposing the first organ to the substance while being perfused, isolating the second organ from the substance, and detecting differences in a functional attribute of the first and second organs.

25. The method of claim 20, wherein a downstream sensor monitors a characteristic of the perfusate exiting the venous system of each organ and produces a signal thereby.

26. The method of claim 25, wherein the perfusate is altered in composition, or pressure or flow rate in the fluid conduit in response to the signal.

27. The method of claim 25, wherein the signal is transmitted to a computer which produces an input representing the signal.

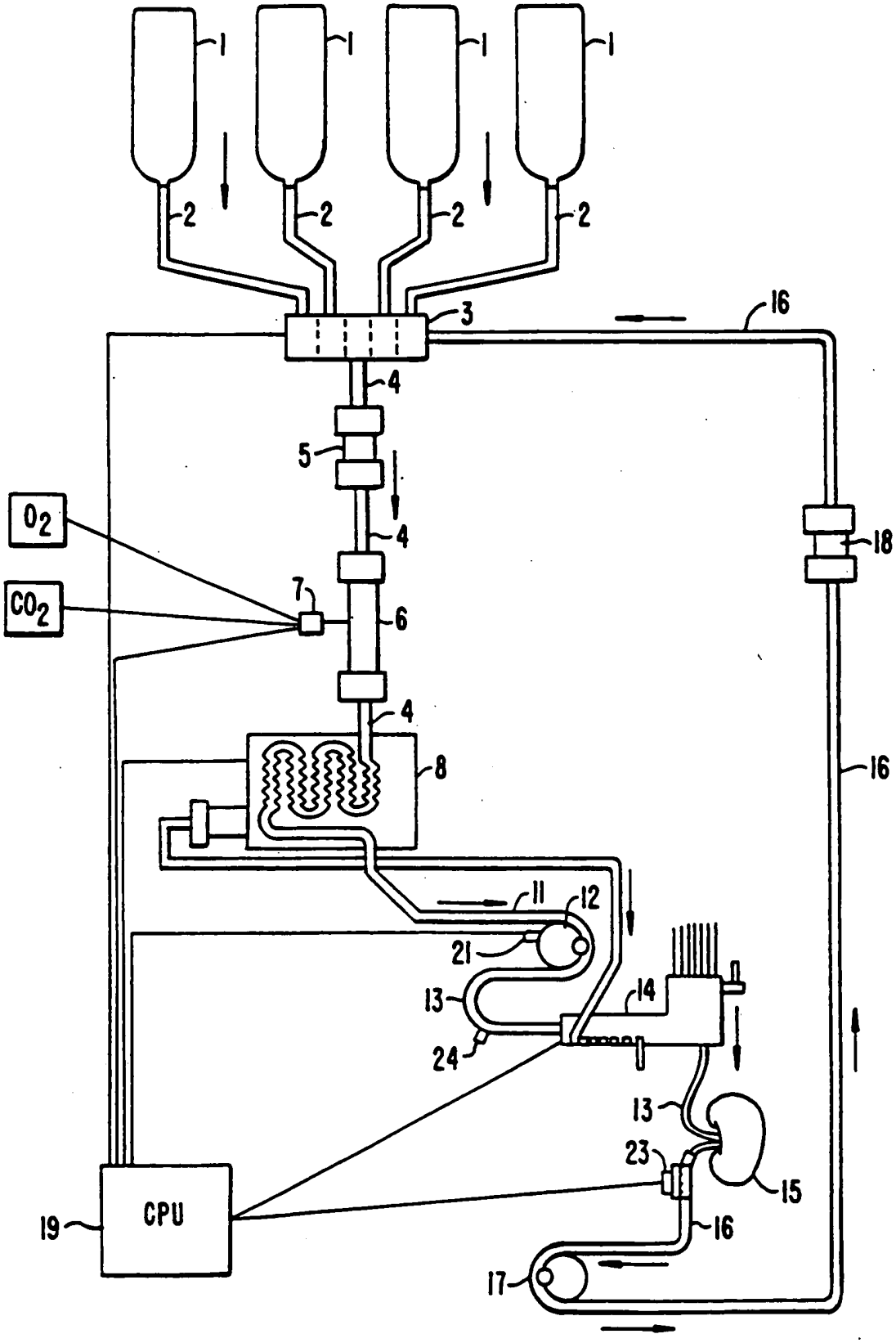

FIG. 2.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/08810

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 5,051,352 (MARTINDALE ET AL.) 24 SEPTEMBER 1991, COLUMNS 14 AND 15 ALL.	5-27
A	US, A, 5,141,847 (SUGIMACHI ET AL.) 25 AUGUST 1992.	1-27
A	US, A, 4,618,586 (WALKER) 21 OCTOBER 1986, SEE ENTIRE DOCUMENT	1-27
A	US, A, 4,242,883 (TOLEDO-PEREYRA) 06 JANUARY 1981.	1-27
A	US, A, 4,029,094 (WINICKI) 14 JUNE 1977.	1-27
A	US, A, 3,914,954 (DOERIG) 28 OCTOBER 1975.	1-27
A	US, A, 3,877,843 (FISCHEL) 15 APRIL 1975.	1-27
A	US, A, 3,604,419 (HAFIA) 14 SEPTEMBER 1971.	1-27
A	EP, A, 01 25847 (RENEAU) 21 NOVEMBER 1984, ENTIRE DOCUMENT.	1-27